## REMARKS

The following is in response to the Official Action dated 27 March 2008. Claims 1 and 12-29 are pending.

In this response, the title of the application is modified to correct a spelling error. Claims 1 and 12 have been amended to clarify the definition of $R^1$. Claim 1 has also been amended to correctly read "$C_{2-6}$alkenyl" and "$C_{2-6}$alkenoxy", as discussed below. Claim 1 has also been amended to delete the phrase "optionally substituted by $C_{1-6}$alkyl, halogen or -$C_{1-6}$alkyl$C_{1-6}$alkoxy" for clarity, as discussed below. Claims 22, 25 and 28 have been amended to read "human" instead of "host". Basis for this amendment can be found on page 16, line 33. No new matter is added hereby.

**1. Objections to the specification:**

This application entered prosecution in the US as a US National Stage Application of PCT Application No. PCT/EP2003/011423 filed 14 October 2003, which claims priority from GB0224084.4 filed 16 October 2002. The PCT Application was filed with all its pages, including pages 5, 14, 20, 27 and 45 of the specification, and lacked any blank pages. This PCT Application published as WO 2004/035556. Attached is a copy of the WO Publication which will provide the pages apparently not included in the transmission of the application from the receiving office to the US PTO.

Please contact the applicant's attorney listed below if further material is needed to effectively examine the application. Otherwise, we hope that this submission is sufficient to address the objection relating to the missing pages.

**2. Claims 22, 25 and 28 are compliant with 35 USC 112, 1st ¶.**

Claims 22, 25 and 28 were objected to under 35 USC 112, 1st ¶. These claims relate to methods of treating "diseases of the upper respiratory tract". These claims are, in fact, **not** related to methods of treating "any and all diseases and/or conditions associated with histamine H3 activity" as asserted by the examiner. The Examiner is respectfully directed to a definition of diseases of the respiratory tract in the description on page 15, line 12 to 15 which includes "asthma (including allergic and non-allergic), allergic rhinitis, sinusitis, bronchitis (including chronic bronchitis), bronchiectasis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis." As discussed below, these diseases are implicated with histamine H3 activity.

The relationship between histamine H3 activity and its physiological function, and thus diseases associated with this function is described in the specification, including references to scientific literature to support the rationale. These scientific documents were published at the priority date of the present patent application. For example, the Examiner is directed to page 14, line 41 to page 15, line 9. Subsequent work has shown that activation of histamine H3 receptors in human nasal mucosa inhibits sympathetic vasoconstriction [Varty *et al.*, *Eur. J. Pharmacol.*, 484:83-89, (2004)]. Further evidence for the contribution of H3 receptors to histamine-induced nasal blockage is provided by histamine nasal challenge studies performed on normal human subjects [Taylor-Clark *et al.*, *Br. J. Pharmacol.*, 144, 867-874, (2005)],. While further work may disprove such relationship, ample support for the H3 mechanism is within the knowledge of those skilled in the art. A copy of each of these scientific papers is included for the Examiner's convenience.

The Examiner has stated that no screening protocols are ever described in the specification. In response, the Examiner is directed to page 129, line 11 to page 132, line 40, where a histamine H3 functional antagonist assay and a histamine H1 functional antagonist assay are described in detail. The results using the assays described for exemplified compounds are found at

page 132, line 22-40, of the specification. The results of the conducted studies using these assays well represent the scope of the claimed genus, thus enabling the ability to determine the $pK_b$ of the compounds within the claimed genus. Specific examples include Examples 255 and 259 having a $pK_b$ greater than 9, and Eaxmpels 256, 258, 260, 266 and 268 all having a $pK_b$ greater 8.4.

Inlight of the details provided in applicant's specification, applicant respectfully asserts that the combination of histamine activity and its relationship to certain diseases is well supported by scientific evidence. The compounds now claimed, which have *in vitro* data showing potency at the H3 receptor, provide the skilled person with a well defined genus of compounds, the means with which to make such compounds, a protocol for effectively demonstrating activity, and thus the information necessary to make and use the claimed invention within the requirements of United States Patent Law.

Under these circumstances, it respectfully asserted that the scope of each of claims 22, 25 and 28 is enabled under 35 USC 112, 1st ¶. Thus, Applicant's respectfully request that this rejection be withdrawn.

**3. Rejection of Claims 1, 12-19 and 21-29 under 35 USC 112, 2nd ¶.**

**a. Claims 1,12-19 and 21-29 Complies with 112, 2nd ¶ define $R^1$.**

The Applicant is unsure as to the precise nature of the objection raised by the Examiner. However, the variable $R^1$ is defined in the claim as "phenyl" which may be optionally substituted by a selection of substituents.

**b. $R^1$ is a substituent of formula (I)**

Again, Applicant is unsure as to the precise nature of the objection raised by the Examiner. However, the variable $R^1$ is defined in the claim as "phenyl" which may be optionally substituted by a selection of substituents. Further, the variable $R^1$ appears on the left hand side of the markush structure of formula (I) as it appears in claim 1. $R^1$ is connected to substituent Z.

**c. "$C_{1-6}$alkenyl" has been corrected**

The term "$C_{1-6}$alkenyl" clearly contains an error. The term should read "$C_{2-6}$alkenyl", because a person skilled in the art would instantly realize that two carbon atoms are required to form a double bond, and therefore that $C_1$alkenyl cannot exist. Thus, this is an obvious error, and appropriate correction is made herein.

**d. "$C_{1-6}$alkenoxy" has been corrected**

The term "$C_{1-6}$alkenoxy" clearly contains an error. The term should read "$C_{2-6}$alkenoxy", because a person skilled in the art would instantly realize that two carbon atoms are required to form a double bond, and therefore that $C_1$alkenoxy cannot exist. Thus, this is an obvious error, and appropriate correction is made herein.

**e. "optionally substituted by $C_{1-6}$alkyl, halogen or -$C_{1-6}$alkyl$C_{1-6}$alkoxy" has been deleted.**

The phrase "optionally substituted by $C_{1-6}$alkyl, halogen or -$C_{1-6}$alkyl$C_{1-6}$alkoxy" was included in claim 1 by mistake, and thus has been deleted, rendering the Examiner's objection moot.

Lastly, applicants appreciate the examiner's thorough and thoughtful review of the application. Further, applicant's acknowledge the allowablity of claim 20. It is respectfully asserted that, in light of the amendments and clarification made herein, that the application is in condition for allowance. Should any minor points exist which preclude allowance of this application, the examiner is encouraged to contact the applicant's attorney at the number listed below.

The Commissioner is hereby authorized to charge any fees required or

credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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